The effect of inhaled and oral dextromethorphan on citric acid induced cough in man

T. J. GRATTAN, A. E. MARSHALL, K. S. HIGGINS & A. H. MORICE
Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Sheffield S10 2JF

1   Dextromethorphan is a widely used antitussive agent which is a non-narcotic codeine analogue. We have investigated whether inhaled administration of dextromethorphan provides antitussive activity in a citric acid induced cough model.

2   Twenty normal subjects underwent repeated cough challenge with 5% citric acid. Subjects were studied on six occasions. Study medication consisted of oral dextromethorphan 30 mg or oral matched placebo or 1, 3 and 30 mg inhaled dextromethorphan or matched inhaled placebo. Cough challenge was administrated 10 min after study medication and hourly thereafter up to 250 min.

3   No significant differences were seen between baseline cough responses. Oral dextromethorphan (30 mg) produced a mean percentage reduction in cough of 38% ($P < 0.002$), which remained significant at 250 min. Inhaled dextromethorphan had no clinically significant effect although activity at later time points was not excluded. The antitussive effect of oral dextromethorphan is confirmed with prolonged inhibition of induced cough. It is possible that dextromethorphan or its active metabolites act centrally to inhibit the cough reflex.

Keywords   cough reflex   antitussive dextromethorphan   citric acid

Introduction

Dextromethorphan is a dextro-isomer of levorphanol (dextro-3-methoxy-*N*-methyl morphinian hydrobromid), a non-narcotic codeine analogue. In man orally administered dextromethorphan has been shown to cause a significant reduction in cough frequency in patients with chronic pathological cough [1]. A similar efficacy in experimentally induced cough in human subjects using a citric acid aerosol has been demonstrated [2–5].

Dextromethorphan exhibits polymorphic metabolism via the enzyme P4502D6 [6], with 10–20% of the population being 'slow' metabolizers. In fast metabolizers dextromethorphan is rapidly *O*-demethylated by the liver to a proposed active metabolite dextrorphan [7] which also has known antitussive activity [8]. Peak plasma levels of dextromethorphan occur approximately 2 h after oral administration and it has a half-life of 2.5–3.9 h [9].

Dextromethorphan binds to two sites in the brain, a high and a low affinity site [10] which are distinct from opioid and other neurotransmitter binding sites. Previous studies using a guinea pig cough model have demonstrated that dextromethorphan may be up to 100 times more potent when given by the pulmonary route compared with oral or i.p. administration [11]. Thus a

local action within the airways may be responsible for some of the antitussive properties of dextromethorphan. In this study we have evaluated the antitussive effect of inhaled dextromethorphan in healthy human volunteers with citric acid-induced cough.

Methods

Twenty normal subjects (11 female, mean age 25 years, range 21–45) were studied using an inhalation cough challenge from a breath activated dosimeter (Mefar, Brescia, Italy). During inspiration the dosimeter delivered a 1 s nebulization of 5% citric acid (dose delivered approximately 33 μmol citric acid). Cough was assessed over the minute following each challenge and challenge was repeated five times. Individuals were screened on two occasions and only those subjects with a reproducible cough response of between 5 and 15 coughs were accepted into the study protocol. The study was approved by the local ethics committee and subjects gave informed consent.

Subjects were asked to return to the clinic on six occasions at the same time of day. Each study day was

separated by at least 24 h and on each occasion a base-line cough challenge was performed to ensure that cough sensitivity had not altered between study days. Fifty minutes after baseline cough challenge subjects received in a randomised single-blind protocol the study medication. Oral medication consisted of 10 ml of 0.9% saline placebo or dextromethorphan HBr 30 mg made up in 10 ml saline. Inhaled medication was delivered by nebulizer (System 22 high flow compressor, CR60 nebulizer) driven at 7 1 min^{-1}. Saline (3 ml of 0·9%) was used as placebo and dextromethorphan HBr 1 mg, 3 mg, 30 mg were used as active treatment.

Cough challenge was repeated at 10, 70, 130, 190 and 250 min after the start of drug administration. Four hours after the 30 mg dextromethorphan HBr dose a urine sample was obtained for analysis of dextromethorphan metabolites. The degree of oral anaesthesia and irritation was assessed 1 h after drug administration by visual analogue score (zero equals no anaesthesia or irritation, ten equals severe irritation).

Statistical analysis

Statistical analysis was by the paired t-test of the area under the curve comparing the oral placebo with the positive control, 30 mg oral dose of dextromethorphan HBr. Dunnett's test was used to compare the three inhaled doses of dextromethorphan with inhaled placebo and also oral placebo. Subjective data from the visual analogue scores were analysed using Student's t-test.

Results

There was no significant difference between baseline cough response on each of the study days. On both inhaled and oral placebo treatment days subsequent cough challenge was highly reproducible (Figure 1 and Table 1).

The 30 mg oral dextromethorphan produced a statistically significant ($P < 0.002$) cough reduction when
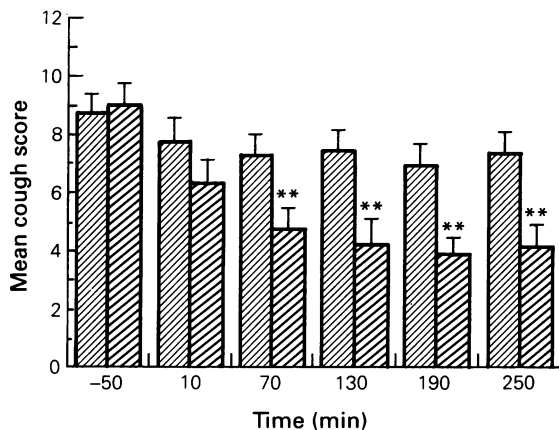
Figure 1 Effect of oral administration of dextromethorphan 30 mg (▨) on citric acid induced cough compared with placebo (▨). Values are mean ± s.e. mean.* $P < 0.002$.

Table 1 Effect of inhaled dextromethorphan on mean cough frequency (95% confidence limits) following citric acid-induced cough

Time post-dose (min)	Dose (mg)	Mean cough	95% confidence lower	upper
10	1	7.4	-1.9	2.8
10	3	7.8	-1.4	3.4
10	30	8.1	-1.1	3.7
70	1	6.6	-2.1	1.8
70	3	6.7	-1.7	2.3
70	30	6.3	-2.1	1.9
130	1	5.6	-3.3	0.9
130	3	5.8	-2.8	1.4
130	30	6	-2.7	1.6
190	1	6.4	-2.2	1.4
190	3	6.4	-2.1	1.6
190	30	5.4	-3.1	0.6
250	1	6.1	-3.1	0.7
250	3	6.5	-2.4	1.4
250	30	5.5	-3.3	0.5

compared with placebo at all time points except for the first post-treatment challenge. Mean percentage reduction in cough was 38% for these time points. In contrast there was little significant difference between the inhaled dextromethorphan and placebo although a difference between 30 mg oral and inhaled could not be excluded particularly at later time points (Table 1).

Visual analogue score of 30 mg oral and inhaled doses demonstrated significantly greater anaesthesia (mean VAS 5.3 vs 2.3, $P = 0.012$) and irritation (mean VAS 4.8 vs 1.1, $P = 0.0011$) with inhaled medication.

Urine samples were obtained from 18 subjects 4 h after receiving 30 mg dextromethorphan orally. Ratio of dextromethorphan to dextrorphan was less than 0.3 in all subjects indicating a fast metabolizer status [12].

Discussion

In this study we have demonstrated that inhalation challenge using citric acid is a highly reproducible index of the cough reflex, provided that the study population is selected to exclude those with no response and those with poorly reproducible evoked cough. The reduction in cough response seen between baseline challenge and t = 10 is not unexpected and is in agreement with our previous observations of the high susceptibility of the citric acid cough challenge to initial tachyphylaxis [13]. By conducting the baseline challenge 60 min before the initial post-treatment challenge, and by restricting the frequency of subsequent challenges to 60 min intervals, we have been able to minimise this effect.

We have confirmed the previously reported efficacy of oral dextromethorphan in producing significant reduction of citric acid induced cough [2] and in this study the reduction in evoked cough continued to be significant at 4 h post-dosing. This effect cannot be explained by delayed metabolism of dextromethorphan since the metabolic ratio of all of our subjects fell into the fast metabolizer group. Thus the adminis-

tration of oral dextromethorphan produces a prolonged antitussive action in man.

The lack of efficacy of inhaled dextromethorphan, and for inhaled opiates, reported in a similar study using a capsaicin cough model [14], is surprising in view of the superior efficacy shown for both inhaled dextromethorphan [11], and inhaled opiates in the guinea-pig model of citric acid induced cough [15]. Evidence from the rat, an obligate nasal breather like guinea-pigs, suggests that absorption can occur from the nasal cavity directly into the CSF [16], and there is also evidence of direct absorption of progesterone and oestradiol in primates [17]. It is therefore possible that in the guinea-pig cough model, there is direct transport of antitussive agent from the nasal cavity to the CSF following inhalation. This could result in elevated levels of drug within the brain, compared with an equivalent dose administered by other routes, and could account for the apparent increase in potency.

In the present study, dextromethorphan was delivered in a nebulized solution via the mouth, and whilst the majority of the dose was probably swallowed, approximately 10% will have been locally deposited in the airways [18]. The lack of effect of high concentrations of dextromethorphan within the airways argues against peripheral dextromethorphan receptors being important in the modulation of the cough reflex.

The degree of oral anaesthesia produced by oral dextromethorphan was significantly less than that seen with a similar inhaled dose. This argues strongly that the antitussive effect of dextromethorphan is specific and not due to a local analgesic effect of the compound.

In conclusion we have demonstrated that oral dextromethorphan is a potent and long lasting antitussive agent, whereas the inhaled drug produces no significant reduction in the cough reflex. Further studies will be required to determine the precise therapeutic half-life of this agent in slow and fast metabolizers so that the effect of dextromethorphan metabolites on the cough reflex may be determined.

References

1 Cass LJ, Frederick WS. Quantitative comparison of cough-suppressing effects of Romilar and other antitussives. *J lab clin Med* 1956; **48**: 879–885.

2 Bickerman HA, German E, Cohen BM. The cough response of healthy human subjects stimulated by citric acid aerosol. *Am J med Sci* 1957; **234**: 191–205.

3 Packman EW, Ciccone PE. The utility of artificially induced cough as a clinical model for evaluating long-lasting antitussive drug combinations. *Am Pharm* 1983; **155**: 42–48.

4 Packman EW, London SJ. The utility of artificially induced cough as clinical model for evaluating antitussive combinations. Part 1: Liquid and solid formulations of systemic drugs. *Curr Ther Res* 1977; **21**: 855–866.

5 Empey DW, Laitinen LA, Young GA, Bye CE, Hughes DTD. Comparison of the antitussive effects of codeine phosphate 20 mg, dextromethorphan 30 mg and noscapine 30 mg using citric acid induced cough in normal subjects. *Eur J clin Pharmac* 1979; **16**: 393–397.

6 Larrey D, Amouyal G, Tinel M, Letteron P, Berson A, Labbe G, Pessayre D. Polymorphism of dextromethorphan oxidation in a French population. *Br J clin Pharmac* 1987; **24**: 676–679.

7 Rachmander G, Williams FD, Emele JF. Determination of dextrorphan in plasma and evaluation of bioavailability of dextromethorphan hydrobromide in humans. *J pharm Sci* 1977; **66**: 1041–1048.

8 Benson WB, Stefko PL, Randal LO. Comparative pharmacology of levorphan, racemorphan and dextrorphan and related methyl ethers. *J pharmac exp Ther* 1953; **109**: 189–200.

9 Dixon R, Carbone JJ, Mohacsi E, Perry C. Dextromethorphan: Radioimmunoassay and pharmacokinetics in the dog. *Res Comm Chem Path Pharm* 1978; **22**: 243–255.

10 Musacchio JM, Klein M. Dextromethorphan binding sites in guinea pig brain. *Cell mol Neurobiology* 1988; **8**: 149–156.

11 Callaway JK, King RG, Boura ALA. Evidence for peripheral mechanisms mediating the antitussive actions of opioids in the guinea-pig. *Gen Pharmac* 1991; **22**: 1103–1108.

12 Zhang Y, Britto MR, Valderhaug KL, Wedlund PJ, Smith MD. Dextromethorphan: Enhancing its systemic availability by way of low dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmac Ther* 1992; **51**: 647–655.

13 Morice AH, Higgins KS, Yeo WW. Adaptation of cough reflex with different types of stimulation. *Eur resp J* 1992; **5**: 841–847.

14 Fuller RW, Karlson JA, Choudry NB, Pride NB. Effect of inhaled and systemic opiates on responses to inhaled capsaicin in Humans. *J appl Physiol* 1988; **65**: 1125–1130.

15 Karlson JA, Lanner AS, Persson CGA. Airway opioid receptors mediate inhibition of cough and reflex bronchoconstriction in guinea pigs. *J Pharmac exp Ther* 1990; **252**: 863–868.

16 Sakane T, Akizuki M, Yamishita S, Nadai T, Hashida M, Sekaki H. Transport of a drug to the cerebrospinal fluid directly from the nasal cavity: The relation to lipophilicity of the drug. *Chem Pharm Bull* 1991; **39**: 2456–2458.

17 Kumar TCA, David GFX, Sankanarayanan A, Puri V, Sundram KR. Pharmacokinetics of progesterone after its administration to ovariectomised rhesus monkeys by injection, infusion, or nasal spraying. *Proc Natl Acad Sci USA* 1982; **79**: 4185–4189.

18 Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered dose inhaler. *Br J dis Chest* 1986; **79**: 361–367.